# Is it possible to increase detection rate of esophageal precancer or cancer lesions in the high-risk population?

**Yiu-Tai Li[a], Wen-Ling Lee[b,c,d], Peng-Hui Wang[d,e,f,g,*]**

*[a]Department of Obstetrics and Gynecology, Kuo General Hospital, Tainan, Taiwan, ROC; [b]Department of Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan, ROC; [c]Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan, ROC; [d]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [e]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [f]Female Cancer Foundation, Taipei, Taiwan, ROC; [g]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC*

Many cancers are considered the highly lethal diseases, contributing to continuously increased health and economic burden worldwide.[1–4] Although the research and treatment for these highly lethal cancers progresses rapidly, the outcome is still disappointing. There are many reasons that can explain the causes about the worse outcomes of these highly lethal cancers. Delayed diagnosis and diagnosis at the advanced stage may be one of the most critical causes, since these highly lethal disease often present vague and nonspecific symptoms, and sometimes totally free of symptoms or late onset of clinical symptoms of these diseases, and additionally, clinically, the lack of efficient disease markers and absence of cost-effectiveness and friendly or convenient screening methods can be used for general population and even for high-risk population. All result in the loss of change to cure these diseases during their early stage status.[1–4] Among these cancers, esophageal cancer (EC) is frequently discussed, since advanced EC either as squamous cell carcinoma (SCC) type or adenocarcinoma types has a very poor prognosis with a 5-year overall survival rate less than 20%.[5] To overcome the big gap between an early identification of cancers at the early stage in theory and a late diagnosis of cancers at the advanced stage in the real world, it is urgent to use an effective screening tool or apply the effective preventive strategy for these highly lethal diseases. With continuous progress of biotechnology, the results of some are relatively promising. These strategies include the development of novel blood biomarkers, the advanced technology of diagnostic tools such as endoscopy and artificial intelligence-assisted endoscopy in the diagnostic work-up of precancer and cancer lesions of esophagus (esophageal intraepithelial neoplasm [EIN] and EC).[5] Blood biomarkers for EIN or EC have been investigated for many years, and with the aids of several emerging technologies, blood screening tests are reported to achieve a relatively acceptable and good performance for the early diagnosis of EIN or EC.[5] However, similar to blood biomarker as screening tools applicable for epithelial ovarian cancer or other benign and malignant diseases, validation is still arguable and the reproducibility is far away from the use in the routine clinical practice due to high false positive and negative rates.[5–8] Additionally, nearly all studies enrolled a relatively small sample size of patients and cut-off of the values or detection threshold value in the different blood biomarkers for the aforementioned diseases vary greatly.[6–8]

Based on the limited roles of blood biomarkers in the aids for early detection of EIN or EC, the continuous development of advanced endoscopic imaging system, such as esophagogastroduodenoscopy (EGDS), has become much acceptable for the aforementioned purpose.[5] In fact, it is reported that EGDS is the gold standard test for EIN and EC.[5] However, EGDS is not a totally noninvasive diagnostic tool and the physicians-related skills and the limitations of visibility and resolution of imaging systems may make the diagnosis challenging. We are happy to introduce the recent publication in the October issue of the *Journal of the Chinese Medical Association*, and the authors attempted to evaluate the effectiveness of image-enhanced endoscopy (IEE) in the detection of EIN or EC for the high-risk population, such as history of hypopharyngeal squamous cell carcinomas (HPSCC) and newly-diagnosed HPSCC.[9]

The authors retrospectively enrolled 99 patients (69 with history of HPSCC and 30 with newly-diagnosed HPSCC) to evaluate the role of Lugol chromoendoscopy (LCE) after the routine white-light image (WLI) and narrow-band image with magnification (NBI-M) for the aid to detect EIN and/or early-stage EC.[9] Combination of all three procedures was called as IEE by authors.[8] Using the WLI, NBI-M, and LCE (IEE) during the EGDS examination, the authors found a 31% of positive rate (n = 31), including 11 with tumor in situ (Tis), 14 with T1 tumor, 2 with T2 tumors, and 4 with T3 tumors based on clinical tumor classification.[8] Additionally, among 69 patients with history of HPSCC, the authors found that one-third of patients develop secondary primary EIN or EC during the follow-up.[9] Seven patients (30.4%) were Tis; 47.8% were T1 (n = 11); 8.7% were T2 (n = 2); 13% were T3 (n = 3); and none was T4.[9] Furthermore, more than two-thirds (69.6%, n = 16) of patients were asymptomatic. All suggest that the application of EGDS with IEE for screening in HPSCC patients, regardless of past history and newly diagnosed, is a very effective tool for the clinical utility.[8] Moreover, the authors proposed routine

*Address correspondence. Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 1075-1077.

Received October 4, 2021; accepted October 4, 2021.

doi: 10.1097/JCMA.0000000000000635.

surveillance via EGDS with IEE may help identify EIN as well as early-stage EC in both past and newly-diagnosed HPSCC patients.[9] With an increase of an early diagnosis of EIN and early-stage EC, the patients may have a better chance to survive after treatment.[9] The current study is interesting and worthy of further discussion.

Similar to patients with Barrett's esophagus prone to developing EIN and EC during their lives,[5] in the current study, the authors found that patients with past or newly-diagnosed HPSCC had a higher risk of synchronous EIN/EC or subsequent development of EIN/EC.[9] As shown in the current study,[9] more than one-fourth of the newly-diagnosed HPSCC patients have a synchronous EIN/EC (10% for invasive EC and 16.7% for EIN).[9] It is very important that all patients with a newly-diagnosed HPSCC should undergo the detailed and thorough evaluation of the upper aerodigestive tract and lung, because of high incidence or high prevalence (>25%) of synchronous or metachronous SCC in oral cancer patients based on the current study.[9] In fact, surveillance programs of the upper aerodigestive tract and lung cancers are mandatory to detect synchronous or metachronous SCC, including EC at early stages.[10] Since the risk of lymph node metastases of superficial EC is related to the depth of invasion, the diagnosis of early lesions is desirable and the patients can be managed successfully with minimally invasive treatments, such as endoscopic ablation therapy.[10] All emphasize the importance of "accurate" and "non-missed" diagnosis of EIN/early-stage EC. As shown before, the reliability and reproducibility of blood biomarkers in the detection of EIN/EC is questionable, contributing to the critical role of endoscopic recognition of EIN and early-stage EC.[5] However, endoscopic recognition of EIN/early-stage EC is challenging, as lesions often pass unrecognized with standard WLE.[5] Studies reported that the missing rate may be up to 40% of early EC, even though the endoscopic examination was performed in the high-risk populations.[5] To overcome the limitation for the diagnosis of EIN/early-stage EC from the endoscopic procedures, the standard Seattle protocol with random 4-quadrant biopsies every 2 cm should be performed.[5] However, the Seattle protocol is a very expensive, time-consuming and unpractical procedure, and adherence rate of endoscopists was poor.[5] Additionally, since mucosa covering the entire esophagus may harbor EIN/EC, it is nearly impossible to perform multiple biopsies as unmeasurable times. It needs an enhanced technology to guide and reveal the "lesions" during the endoscopic examination, contributing to the development of many new novel endoscopic techniques. Similar to the authors' mention, the effectiveness has been investigated continuously. These IEE systems include dye spray chromoendoscopy (DSCE), virtual chromoendoscopy (VCE), confocal laser endomicroscopy, and volumetric laser endomicroscopy.[5,10–12] With the aids of these novel endoscopic techniques, the endoscopic examination may be much humanized and the risk of missed diagnosis or the overdone biopsies may be minimized.[5]

In the current study, the authors used steadily spraying approximately 10 to 20 mL of iodine staining (Lugol's solution) over the entire esophagus via dye-spraying catheter to perform Lugo chromoendoscopy (LCE).[9] This procedure is not new. A recent meta-analysis has shown its feasibility.[11] A total of 1911 patients from 12 studies showed that for the diagnosis of EIN/EC, LCE had the pooled sensitivity, specificity, positive likelihood ratio (LR), and negative LR were 0.92 (95% CI: 0.86-0.96), 0.82 (95% CI: 0.80-0.85), 5.4 (95% CI: 3.2-9.1), and 0.13 (95% CI: 0.08-0.23), respectively.[11] All supported the authors' finding to show the need of using EGDS with IEE in the routine surveillance for those past and newly-diagnosed HPSCC patients.[8] However, there are many dyes that can be sprayed on the luminal esophageal surface to obtain selective mucosal uptake (vital staining, such as methylene blue or Lugol's solution) or mucosal pattern enhancement (contrast staining, such as indigo carmine and acetic acid).[5] We are wondering why the authors selected "Lugol's solution, although Lugol's iodine dye spray is used in the diagnosis of EIN/EC as SCC type appears as Lugol-voiding lesion.[5] This question is raised based on the results of a recent meta-analysis.[12] The conclusion showed the use of acetic acid as a dye might be an alternative choice in the detection of EIN/EC compared to the use of Lugol's solution based on nine studies and 1379 patients enrolled, although no head-to-head comparison studies have been conducted. The results showed that acetic acid (1.5-2.5%) chromoendoscopy (AACE) showed a pooled sensitivity of 0.92 (95% CI: 0.83-0.97), pooled specificity of 0.96, positive LR of 25.0 (95% CI: 5.9-105.3), and negative LR of 0.08 (95% CI: 0.04-0.18) for the diagnosis of EIN/EC, and the diagnostic performance of AACE had at least 6-fold increase compared to the Seattle protocol, suggesting its superiority.[12]

In fact, this application of dye-staining strategy either by AA or by Lugol's solution is very popular in routine clinical practice of gynecologists for the detection the precancer and cancer lesions of the cervix.[13–15] A meta-analysis was conducted to assess and compare the accuracy of visual inspection with AA and Lugol's solution and human papillomavirus (HPV) testing as alternative standalone methods for primary cervical cancer screening in low socio-economic countries, and the results showed visual inspection with Lugol's solution is a simple and affordable alternative to cytology that demonstrates higher sensitivity than visual inspection with AA.[14,15] Therefore, we can fully understand why the authors in the current study selected Lugol's solution as a dye to perform IEE during the EGDS procedure.[9]

Although evidence and the authors' conclusion favored the application of Lugol's iodine dye spray in the aid of diagnosis of EIN/EC during the routine EGDS procedure,[9–12] the use of DSCE (either LCE or AACE) is at the risk of drawbacks in clinical practice, including the need for dedicated equipment, impossibility to study superficial vascularity, difficulty to obtain uniform mucosal coating, and the duration of the procedure.[5] Additionally, dye spraying using the agent as Lugol's iodine may induce the allergic reaction, and also carry the risk of aspiration and chest discomfort and possible pneumonia.[5] By contrast, the above-mentioned limitations are not present in the screening of cervical precancer and cancer lesions mediated by colposcopy or pure visuality.[13–15] All suggest that the approach via LCE-mediated IEE in the aid of diagnosing EIN/early-stage EC may not be a better choice.

Recently, the other tool, such as VCE, has become more and more popular based on similar effect of dyes or stains to provide contrast enhancement of the mucosal surface and blood vessels without the use of stains or dyes.[5] Therefore, the limitations of IEE by LCE can be overcome successfully.

Taken together, we do not argue the value of IEE by LCE for the aid to provide a better chance in the detection of EIN/early-stage EC in the high-risk population. By contrast, we encourage more and more studies focusing on this topic to improve the diagnostic accuracy for this highly lethal disease.

## ACKNOWLEDGMENTS

This article was supported by grants from the Taiwan Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 109-2314-B-075B-014-MY2 and MOST 110-2314-B-075-016-MY3), and Taipei Veterans General Hospital (V110C-082, and VGH109E-005-5). The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

## REFERENCES


1. Lu HW, Chen CC, Chen HH, Yeh HL. The clinical outcomes of elderly esophageal cancer patients who received definitive chemoradiotherapy. *J Chin Med Assoc* 2020;**83**:906–10.
2. Lee WL, Wang PH. Immunology and ovarian cancers. *J Chin Med Assoc* 2020;**83**:425–32.
3. Huang CY, Cheng M, Lee NR, Huang HY, Lee WL, Chang WH, et al. Comparing paclitaxel-carboplatin with paclitaxel-cisplatin as the frontline chemotherapy for patients with FIGO IIIC serous-type tubo-ovarian cancer. *Int J Environ Res Public Health* 2020;**17**:2213.
4. Li YT, Liu CH, Wang PH. Treatment for recurrent epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 2021;**60**:803–4.
5. Visaggi P, Barberio B, Ghisa M, Ribolsi M, Savarino V, Fassan M, et al. Modern diagnosis of early esophageal cancer: from blood biomarkers to advanced endoscopy and artificial intelligence. *Cancers (Basel)* 2021;**13**:3162.
6. Lee WL, Wang PH. Aberrant sialylation in ovarian cancers. *J Chin Med Assoc* 2020;**83**:337–44.
7. Horng HC, Su MH, Wang PH. Does any serum marker predict the ovarian endometrioma accompanied with or without deep infiltrative endometriosis? *J Chin Med Assoc* 2020;**83**:797–8.
8. Huang CY, Cheng NM, Wang PH. Risk factors associated with epithelial ovarian cancer in women with endometriosis. *Taiwan J Obstet Gynecol* 2020;**59**:353–5.
9. Huang YW, Wang YP, Lee TL, Chang CF, Hou MC, Tai SK, et al. Image-enhanced endoscopy for detection of second primary esophageal neoplasms in patients with hypopharyngeal cancer: prevalence, risk factors, and characteristics. *J Chin Med Assoc* 2021;**84**:963–8.
10. Safatle-Ribeiro AV, Baba ER, Faraj SF, Rios JT, de Lima MS, Martins BC, et al. Diagnostic accuracy of probe-based confocal laser endomicroscopy in Lugol-unstained esophageal superficial lesions of patients with head and neck cancer. *Gastrointest Endosc* 2017;**85**:1195–207.
11. Morita FH, Bernardo WM, Ide E, Rocha RS, Aquino JC, Minata MK, et al. Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: a systematic review and meta-analysis. *BMC Cancer* 2017;**17**:54.
12. Coletta M, Sami SS, Nachiappan A, Fraquelli M, Casazza G, Ragunath K. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. *Gastrointest Endosc* 2016;**83**:57–67.e1.
13. Srisuttayasathien M, Manchana T. Adherence to follow-up in women with cervical intraepithelial neoplasia grade 1. *Taiwan J Obstet Gynecol* 2021;**60**:56–9.
14. Catarino R, Schäfer S, Vassilakos P, Petignat P, Arbyn M. Accuracy of combinations of visual inspection using acetic acid or lugol iodine to detect cervical precancer: a meta-analysis. *BJOG* 2018;**125**:545–53.
15. Fokom-Domgue J, Combescure C, Fokom-Defo V, Tebeu PM, Vassilakos P, Kengne AP, et al. Performance of alternative strategies for primary cervical cancer screening in sub-Saharan Africa: systematic review and meta-analysis of diagnostic test accuracy studies. *BMJ* 2015;**351**:h3084.